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(71) Applicant *(for all designated States except US)*: ORION-YHTYMÄ OY [FI/FI]; Orionintie 1, FIN-02200 Espoo (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: URTTI, Arto [FI/FI]; Isokaari 29, FIN-70420 Kuopio (FI). HIRVONEN, Jouni [FI/FI]; Telakkakuja 3 A 6, FIN-70100 Kuopio (FI). LEHTONEN, Lasse [FI/FI]; Seilimäki 20 H 24, FIN-02180 Espoo (FI). ANTILA, Saila [FI/FI]; Mannerheimintie 146 A 3, FIN-00270 Helsinki (FI).

(74) Agent: ORION CORPORATION; Orion Pharma, Patent Service, P.O. Box 65, FIN-02101 Espoo (FI).

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(54) Title: TRANSDERMAL COMPOSITIONS CONTAINING LEVOSIMENDAN

(57) Abstract

Transdermal administration of levosimendan or (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof is disclosed. Transdermal preparations of levosimendan can be in the form of e.g. ointment, emulsion, lotion, solution, gel, cream, patch or transdermal delivery device including iontophoretic device.

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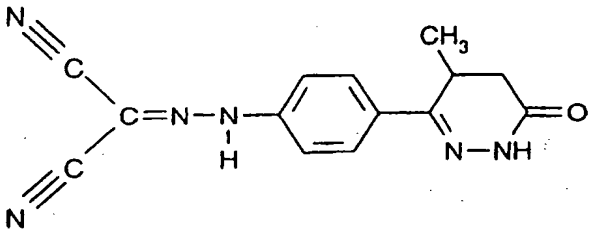
# TRANSDERMAL COMPOSITIONS CONTAINING LEVOSIMENDAN

## Technical field

The invention relates to transdermal preparations containing as an active ingredient levosimendan or a pharmaceutically acceptable salt thereof and to a method of treating heart failure by transdermally administering levosimendan or a pharmaceutically acceptable salt thereof.

## Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I), and the method for its preparation is described e.g. in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. The use of levosimendan in the treatment of myocardial ischemia is described in WO 93/21921. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995.



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It has now been found that therapeutically effective serum levels of levosimendan can be achieved by administering levosimendan transdermally. Transdermal delivery of levosimendan provides a safe method for administering levosimendan to a patient at a desired steady rate.

## Summary of the invention

The present invention provides a transdermal preparation comprising as therapeutically active ingredient (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for transdermal administration of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

Furthermore the present invention provides a method for treating heart failure comprising administering transdermally to a subject in need of such treatment an therapeutically effective amount of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

Detailed description

The transdermal administration of levosimendan or a pharmaceutically acceptable salt thereof can be accomplished for example: (i) by mixing the therapeutically active compound or a pharmaceutically acceptable salt thereof with suitable pharmaceutically acceptable carriers and optionally skin penetration enhancers to form preparations such as ointments, emulsions, lotions, solutions, creams, gels or the like, where preferably a fixed amount of said preparation optionally covered with an impermeable backing layer is to be applied onto a predetermined area of the skin or (ii) by incorporating the therapeutically active substance into patches or transdermal delivery systems according to known technology.

The preparation of suitable transdermal delivery systems is described e.g. in WO 92/21334, WO 92/21338 and EP 413487. Such system may comprise (a) a drug impermeable backing layer and (b) an adhesive layer that fixes the bandage to the skin, wherein the drug is dispersed in the adhesive layer. Alternatively, the system may comprise (a) a drug impermeable backing layer, (b) an adhesive layer and (c) a matrix layer preferably made of a polymer material in which the drug is dispersed. The rate at which the drug is released from the device is here controlled by the polymer matrix. The system may also comprise (a) a drug impermeable backing layer, (b) an adhesive layer, (c) a drug permeable membrane sealed to one side of said backing layer as to define at least one drug reservoir compartment therebetween and (d) a drug or composition thereof within said drug reservoir. In this case the drug in the reservoir is usually in liquid or gel form. The drug permeable membrane controls the rate at which the drug is delivered to the skin.

Iontophoretic transdermal delivery systems according to known technology can also be used in the transdermal delivery of levosimendan. Term "iontophoresis" means using small electric current to increase transdermal permeation of charged drugs. The method is reviewed in e.g. Burnette R., Iontophoresis. In Transdermal Drug Delivery, pp. 247-292, Eds. Guy, R. and Hadgraft, J., Marcel Dekker Inc., New York and Basel, 1989. Iontophoretic transdermal delivery system typically include a first (donor) electrode containing an electrolytically available active compound within a suitable vehicle or carrier, a second (passive) electrode and a power source, the first and second electrodes each being in electrically conductive communication with the power source. The first and second electrodes are being adapted for spaced apart physical contact with the skin whereby, in response to a current provided by the power source through the electrodes, a therapeutic amount of the active compound is administered through the skin to a patient.

Suitable pharmaceutical carriers include those well known in the art of pharmacy for the preparation of topical formulations such as glycols and glycol ethers, polyethylene glycol, propylene glycol, glycerol and glycerol ethers, lower alcohols such as ethanol or isopropanol, water, non-volatile fatty alcohols, e.g. cetostearyl alcohol and cetyl alcohol, N-methylpyrrolidone, vegetable and animal oils, sesame oil, olive oil, wood alcohol ointments, vaseline and paraffin, cellulose derivatives, e.g. methylcellulose, hydroxy propylmethyl cellulose (HPMC) or carboxymethyl cellulose, or mixtures thereof.

Suitable skin penetration enhancers include those well known in the art, for example, $C_2$-$C_4$ alcohols such as ethanol and isopropanol; surfactants, e.g. anionic surfactants such as salts of fatty acids of 5 to 30 carbon atoms, e.g. sodium lauryl sulphate and other sulphate salts of fatty acids, cationic surfactants such as alkylamines of 8 to 22 carbon atoms, e.g. oleylamine, and nonionic surfactants such as polysorbates and poloxamers; aliphatic monohydric alcohols of 8 to 22 carbon atoms such as decanol, lauryl alcohol, myristyl alcohol, palmityl alcohol, linolenyl alcohol and oleyl alcohol; fatty acids of 5 to 30 carbon atoms such as oleic acid, stearic acid, linoleic acid, palmitic acid, myristic acid, lauric acid and capric acid and their esters such as ethyl caprylate, isopropyl myristate, methyl laurate, hexamethylene palmitate, glyceryl monolaurate, polypropylene glycol monolaurate and polyethylene glycol monolaurate; salicylic acid and its derivatives; alkyl methyl sulfoxides such as decyl methyl sulfoxide and dimethyl sulfoxide; 1-substituted

azacycloalkan-2-ones such as 1-dodecylazacyclo-heptan-2-one sold under the trademark AZONE; amides such as octylamide, oleicamide, hexamethylene lauramide, lauric diethanolamide, polyethylene glycol 3-lauramide, N,N-diethyl-m-toluamide and crotamiton; and any other compounds compatible with levosimendan and the packages and having transdermal permeation enhancing activity.

The preparation according to the invention may also include an antimicrobial agent, a preservative, an antioxidant and a pH-controlling agent and other additives known in the art.

Preferred administration rate of levosimendan in the transdermal delivery is within the range of about 1 - 1000 µg/h through a skin area of about 2 - 100 $cm^2$. The daily dose of levosimendan to man is within the range of about 0.1 to 500 mg, preferably 0.5 to 10 mg depending on the age, body weight and condition of the patient. The amount of drug delivered into the skin can be controlled by a number of factors including skin patch size, degree of drug loading, the use of rate controlling membranes, permeation enhancers etc.

## EXPERIMENTS

### Permeation experiments

Transdermal penetration of levosimendan across human skin in vitro was studied with side-by-side diffusion chambers (DC-100, Crown Glass Co., Somerville, NJ) at 25 °C. The receiver phase (3 ml) consisted of blank sodium phosphate buffer (pH 5.0). Each studied saturated levosimendan solution (3ml) was added to the donor side. Levosimendan permeation from the gel-formulation was studied with Franz -diffusion chambers (DC-400, Crown Glass Co., Somerville, NJ) at 25 °C. The volume of donor and receiver phases were 1 ml and 5 ml, respectively. Samples were withdrawn up to 72 h at fixed intervals and levosimendan concentration in samples was determined by HPLC (Beckman System Gold, Beckman Instruments Inc., CA). The HPLC column used was LiChrosorb RP-18 (7 µm, 250 mm x 4 mm), and the mobile phase was 55 % of methanol and 45 % of sodium phosphate buffer at pH 2,1. Detection wavelength was 360 nm and flow rate was 1.2 ml per min. Transdermal flux of levosimendan (µg/h per $cm^2$) across the skin was calculated using linear regression of the straight-line portion of drug permeation vs. time curve, and dividing by the surface area of the skin (0.64 $cm^2$).

The gel formulation of levosimendan was prepared from hydroxy propylmethyl cellulose (HPMC) (2.5 % m/V, average M.W. 100.000; Aldrich Chemical Co., Steinheim, Germany), and ethanol (10 %) and sodium lauryl sulphate (0.01 %) were added to the gel. The permeation results show that levosimendan permeation across human skin in vitro was practically the same from the solution and from the gel prepared from the same solution.

The permeation results are shown in Table 1.

TABLE 1. Permeation of levosimendan across human skin in vitro. Donor formulations buffered to pH 5 with sodium phosphate buffer. SLS = sodium lauryl sulphate, PG = propylene glycol, OA = oleic acid. % = % m/V.

| Donor formulation | Conc. mg/ml | pH | Flux ± SD µg/cm²h | Lag time h |
|---|---|---|---|---|
| water + 90 % ethanol | 3.66 | 5.0 | 7.05 ± 1.11 | 15 |
| water + 40 % ethanol | 1.73 | 5.0 | 0.87 ± 0.21 | 15 |
| water + 10 % ethanol + 0.01 % SLS | 0.061 | 5.0 | 0.43 ± 0.09 | 15 |
| water + 10 % ethanol + 0.01 % SLS HPMC-gel (2.5 %) | 0.061 | 5.0 | 0.48 ± 0.15 | 15 |
| water + 10 % ethanol + 40 % PG + 5 % OA | 1.19 | 5.0 | 16.0 ± 1.62 | 15 |
| water + 0.1 % SLS | 0.061 | 5.0 | 5.25 ± 0.96 | 20 |
| water + 1 % SLS | 0.49 | 5.0 | 25.38 ± 5.46 | 20 |

Permeation from iontophoretic device

Electrodes for iontophoresis were prepared from silver wire and silver chloride (Aldrich-Chemie, Steinheim, Germany). Direct current (0.5 mA/cm²) during iontophoresis was delivered by HP 6181C DC current source (Hewlett-Packard, CA) from the electrodes to the diffusion chambers via salt bridges. Salt bridges were prepared by injecting 1 M NaCl-gel (3 % agar) inside plastic tubing (diameter 4 mm, length 15 cm). Salt bridges prevented direct contact and possible reactions of levosimendan with Ag/AgCl-electrodes. HEPES-buffer at pH 7.4 was used in the receiver phase. Saturated levosimendan

solution (3 ml) in HEPES-buffer (pH 7.4) was added to the donor side. AgCl-cathode was connected via the salt bridge to the donor solution. Positive silver anode was connected via the salt bridge to the receiver solution. The chambers were connected in series as constant DC-current was used. The Ag/AgCl-electrodes could be used continuously for 12 h. The results of this experiment are summarized in Table 2.

TABLE 2. Penetration of levosimendan across human skin in vitro by iontophoresis (constant current 0.5 mA/cm$^2$).

| Donor solution | Conc. mg/ml | pH | Flux ± SD µg/cm$^2$h | Lag time h |
|---|---|---|---|---|
| HEPES-buffer | 0.41 | 7.4 | 2.87 ± 0.57 | 2 |

CLAIMS

1. A transdermal preparation comprising as therapeutically active ingredient (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

2. A preparation according to claim 1 which is in the form of an ointment, emulsion, lotion, solution, gel, cream or patch.

3. A preparation according to claim 1 where the preparation is a transdermal delivery system comprising a drug impermeable backing layer and an adhesive layer where the active ingredient is dispersed in the adhesive layer.

4. A preparation according to claim 1 where the preparation is a transdermal delivery system comprising a drug impermeable backing layer; an adhesive layer and a matrix layer in which the active ingredient is dispersed.

5. A preparation according to claim 4 where the matrix layer is made of a polymer material.

6. A preparation according to claim 1 where the preparation is a transdermal delivery system comprising a drug impermeable backing layer; an adhesive layer; a drug permeable membrane positioned relative to said backing layer so that at least one drug reservoir compartment is defined between said membrane and said backing layer, and the active ingredient or a composition thereof within said drug reservoir.

7. A preparation according to claim 1 where the preparation is a iontophoretic transdermal delivery system.

8. A preparation according to any one of claims 1-7 for use in the treatment of heart failure.

9. A method for treating heart failure comprising administering transdermally to a subject in need of such treatment an therapeutically effective amount of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

10. Use of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for transdermal administration of (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

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PCT/FI 97/00412

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☐ Further documents are listed in the continuation of box C.

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